IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Keith E. Mostov Application No.: 09/818,247 Filed: March 26, 2001 For: LIGANDS DIRECTED TO THE NON-SECRETORY COMPONENT, NON-STALK REGION OF PIGR AND METHODS OF USE THEREOF Customer No.: 20350	Confirmation No. 1580 Examiner: Belyavskyi, Michail Technology Center/Art Unit: 1644 DECLARATION OF DR. JACQUELINE M. GLYNN UNDER 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, JACQUELINE M. GLYNN, hereby declare and state:

1. I received a B.Sc. in Biotechnology from Dublin City University, Dublin, Ireland, in 1989, and received a Ph.D. in Cell Biology from St. Patrick's College, Kildare, Ireland, in 1993. From 1991-1992, while a graduate student at St. Patrick's College, I performed research at the La Jolla Institute for Allergy and Immunology, La Jolla, CA. I held a postdoctoral fellowship at The Scripps Research Institute, La Jolla, CA, from 1993 to 1997.

2. From 1997 to 1998, I was employed as a research scientist at Chiron Technologies, Center for Gene Therapy, San Diego, CA. From 1999 to 2000, I was a research scientist with Epicyte Pharmaceuticals, San Diego, CA. In June 2000, I joined Arizeke Pharmaceuticals, Inc., San Diego, CA ("Arizeke"), as a senior research scientist. Since January 2003, I have been Arizeke's Associate Director of Research. A copy of my C.V. is attached as Exhibit 1.

3. Arizeke is commercializing products based in part on delivery of therapeutic molecules to persons in need thereof by linking the therapeutic molecules to ligands to portions of the polymeric immunoglobulin receptor ("pIgR"). One of my responsibilities at Arizeke is to

coordinate external collaborations and internal research to develop new ligands to portions of pIgR. As part of my work, I have become aware of the captioned patent application (the "'247 application"). I am not an inventor of the '247 application and have no financial interest in it.

4. As stated in the '247 application, once pIgR is transcytosed to the apical surface of a cell, the pIgR undergoes an initial cleavage releasing the bulk of the molecule into the extracellular space. This released portion of the pIgR molecule is known as the secretory component, or "SC." A residual extracellular region of pIgR (the "stalk") remains accessible on the cell surface. Newly-cleaved SC contains a carboxy-terminal region adjacent to the cleavage site which is rapidly degraded by proteases to provide the SC typically found in the lumenal space, such as the mammalian intestine. The region of the SC adjacent to the cleavage site which undergoes further proteolytic digestion or secondary cleavage following the initial cleavage of SC from the intact pIgR molecule is sometimes referred to as the "B region."

5. I understand that the Office Action mailed September 23, 2003 (the "Action"), regarding the '247 application takes the position that, other than for antibodies, the specification does not provide sufficient information to enable a person of skill in the art to make agents that bind to the B region. For example, I understand that the Action considers the specification not to be enabled for the production of non-antibody proteins and peptides that bind the B region. I believe that this position is based on a misperception of the techniques available in the art and the knowledge of the persons of skill in this art.

6. Techniques existed in the art prior to the priority date of the captioned application for rapidly screening libraries of peptides for peptides that can bind to a target of choice, and there are companies that provide such screening. For example, Dyax Corp. (Cambridge, MA) ("Dyax") has large and diverse libraries of peptides that it screens by using phage display technology. Phage display technology was developed in the late 1980s, and permits rapid screening of large numbers of peptides. Persons of skill in the art were well aware before the priority date of the application of the capabilities of phage display to rapidly screen libraries of peptides to identify peptides that bind to any particular target of choice.

7. Arizeke entered into a relationship with Dyax under which Dyax screened Dyax's peptide libraries for peptides that bind to pIgR. The peptides were expressed on phage particles using standard phage display techniques and screened against an immobilized GST-pIgR fusion protein (glutathione-S-transferase, or "GST," is a protein used to enhance production

of a second protein, in this case, pIgR. The techniques used ensure that the proteins the bind the fusion protein bind to the pIgR portion, not to the GST port on.). Referring to Figure 1 of the application, the portion of pIgR fused to the GST comprised all of domain 6 of pIgR, and the carboxyl portion of pIgR domain 5 (the "D6/D5 fusion"). Thus, the D6/D5 fusion protein encompassed both the site of the initial proteolytic cleavage of SC from the stalk, and the B region. For Arizeke's purpose of delivering therapeutics to patients, we chose to look for peptides that could bind to anywhere in this D6/D5 fusion. Persons of skill would recognize that one could readily perform the same screening on a peptide consisting of the B region alone.

8. The peptide libraries were screened in a several step process. First, using standard techniques for such screening, phage were generated which expressed on the phage surface peptides from the library. Phage and peptides which did not bind the immobilized fusion protein were washed away. After several rounds of screening, the peptides that best bound to the pIgR portion of the molecule were selected for further screening.

9. Second, the peptides identified in step 1 were then screened against MDCK cells ("MDCK" cells, or "Madin-Darby canine kidney" cells, are a well-established, commercially available, mammalian cell line that does not naturally express pIgR) that were transfected with either human, rat, or monkey pIgR. This step tested whether the peptides identified in the first screening bound to intact, native pIgR. In some studies, conditions were used to identify peptides that internalized into the cells after binding to pIgR. Using standard techniques, Dyax also identified motifs in the binding peptides, and used them to identify other peptide sequences that would likely result in peptides that bound to pIgR.

10. Dyax has reported the results of the binding studies to Arizeke. A total of 10 peptides were identified that not only bound to the D6/D5 portion of pIgR, but that were also internalized into the MDCK pIgR-expressing cells. Eight additional peptides were identified that bound to the cell surface. Twenty one additional peptides were identified as potential "hits" as

binding to pIgR, but were not further evaluated. A total of '72 additional peptides were identified by motif. Thus, dozens of peptides that bind the D6/D5 reg.on of pIgR were identified.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

3/23/04
Date

Dr. Jacqueline M. Glynn

CURRICULUM VITAE
DR. JACQUELINE M. GLYNN

Education

Institution	Dates	Degrees/Field
The Scripps Research Institute, La Jolla, CA,USA	1993-1997	Postdoctoral Fellow
St. Patrick's College, Maynooth, Co. Kildare, Ireland	1989-1993	Ph.D. in Cell Biology Thesis title: Oncogenes, cell cycle and apoptosis
La Jolla Institute for Allergy and Immunology, La Jolla CA, USA	1991-1992	Graduate research while Ph.D. student at St. Patrick's College
Dublin City University, Ireland	1985-1989	B.Sc. Biotechnology

Employment History

Arizeke Pharmaceuticals Inc., San Diego, CA — **2000-Present**
Associate Director-Research — *January 2003-Present*
Senior Research Scientist — *June 2000-January 2003*

Recombinant protein expression and production systems for gene fusions & new ligand discovery program.

- Oversee all research activities of Cellular & Molecular Biology groups.
- Coordinate research activities from initial proof-of-concept studies with therapeutic proteins though Phase One trials.
- Coordinate external collaborations and internal efforts in area of new ligand discovery.

Epicyte Pharmaceuticals, San Diego, CA — **1999-2000**
Research Scientist

Research and development of human antibody expression in plants

- Demonstrated expression of dimeric IgA in *Trichoplusia ni* larvae using the baculovirus expression system.
- Involved in purification and analysis of antibodies from corn and rice.
- Developed a novel quantitative assay that can be used to determine binding of dimeric IgA to polymeric Immunoglobulin Receptor.
- Developed ELISA to screen patient sera for reactivity to *C. difficile* Toxins A&B.
- Utilized antibody discovery techniques, including phage display, to identify novel antibodies for expression in the plant system.

Chiron Technologies, Center for Gene Therapy, San Diego, CA **1997-1998**
Research Scientist under the supervision of Dr. Jiing-Kuan Yee

Research and development of lentiviral vectors, specifically HIV-based vectors, for gene delivery.

- Constructed vectors with a number of reporter and functional genes utilizing a variety of molecular biology skills.
- Gained experience in culturing numerous human cell types and focused on these as targets for gene delivery.
- Demonstrated initiative in coordinating and conducting collaboration with academic investigators on projects to test the efficacy of lentiviral vectors *in vivo.*
- Initiated and developed research in the area of tissue specific targeting via tissue/cell-specific promoters.
- Experienced in the operation of a BSL-3 lab.

The Scripps Research Institute, San Diego, CA **1993-1997**
Post-doctoral research under the supervision of Dr. D. Mosier

Investigation of the role of apoptosis during HIV-1 infection.

- Characterized the immune response in hu-PBL-SCID mice after HIV infection.
- Addressed the controversy of whether cells die as a result of direct infection or by indirect mechanisms using both in vitro (infectious cell-based assays) and in vivo models e.g. the hu-PBL-SCID mouse model.
- Techniques utilized include in situ hybridization, flow cytometry and in situ apoptosis assays.
- Investigated the role of cytokine profile and HIV co-receptor expression on susceptibility to HIV-induced apoptosis using RNase protection assay, RT-PCR and flow cytometry.
- Numerous presentations at research symposia.

La Jolla Institute for Allergy and Immunology, La Jolla, CA **1991-1992**
St. Patrick's College, Maynooth, Ireland **1989-1991**
Graduate research under the supervision of Dr. Douglas Green & Dr. Thomas Cotter

Studies on the role of oncogenes and cell cycle in apoptosis.

Flemming GmbH, Clare, Ireland **1988**
Undergraduate research under the supervision of Dr. J. J. Tobin

Research and development of diagnostic assays.

Honors/Awards

International Union of Biochemistry, Traveling Scholar Fellowship **1991**

University of California University-wide AIDS Research Program, Two year Individual Fellowship **1995-1997**

Immigrant Status

Resident Green Card Holder

Publications

1. Cotter, T.G., Lennon, S.V., Glynn, J.G., Martin, S.J. 1990. Cell death via apoptosis and its relationship to growth, development and differentiation of both tumor and normal cells. *Anticancer Res.* **10**:1153-1159.
2. Green, D.R., Bissonnette, R.P., Glynn, J.M., Shi, Y. 1992. Activation-induced apoptosis in lymphoid systems. In: *Apoptosis in the Immune System* . (eds) Green, D.R., Academic Press, London. *Semin Immunol* 4:379-388.
3. Shi, Y., Glynn, J.M., Guilbert, L.J., Cotter, T.G., Bissonnette, R.P., Green, D.R. 1992. Role for c-myc in activation-induced apoptotic cell death in T cell hybridomas. *Science.* **257**:212-214.
4. Glynn, J.M., Cotter, T.G., Green, D.R. 1992. Apoptosis induced by Actinomycin D, Camptothecin or Aphidicolin can occur in all phases of the cell cycle. *Biochem Soc Trans.* **20**:84S.
5. Cotter, T.G., Glynn, J.M., Echeverri, F., Green, D.R. 1992. The induction of apoptosis by chemotherapeutic agents occurs in all phases of the cell cycle. *Anticancer Res.* **12**:773-779.
6. Cotter, T.G., Lennon, S.V., Glynn, J.M. Green, D.R. 1992. Microfilament-disrupting agents prevent the formation of apoptotic bodies in tumor cells undergoing apoptosis. *Cancer Res.* **52**:997-1005.
7. Glynn, J.M. 1993. Oncogenes, cell cycle and apoptosis. Doctoral Thesis.
8. Green, D.R., Mahboubi, A., Nishioka, W., Oja, S., Echeverri, F., Shi, Y., Glynn, J. Yang, Y., Ashwell, J., Bissonnette, R. 1994. Promotion and inhibition of activation-induced apoptosis in T-cell hybridomas by oncogenes and related signals. In: *Immunological Reviews.* G. Moller, eds. Munksgaard International Publishers, Munksgaard, Copenhagen. **142**:321-342.
9. Glynn, J., Rochford, R., and Mosier, D.E. 1995. Patterns of cytokine mRNA synthesis in $CD4^+$ T cell clones and susceptibility to HIV-1 infection. IN: *First International Symposium on HIV and Cytokines* (eds.) INSERM (Focus Serie). Reims, France.
10. Glynn, J.M., McElligott, D.L., and Mosier, D.E. 1996. Apoptosis induced by human immunodeficiency virus infection in H9 T cells is blocked by ICE-family protease inhibition but not by a FAS(CD95) antagonist. *J. Immunol.* **157**:2754-2758
11. Rochford, R., Cannon, M.J., Sabbe, R.E., Adusumilli, K., Picchio, G., Glynn, J.M., Noonan, D.J., Mosier, D.E., and Hobbs, M.V. 1997 Common and idiosyncratic patterns of cytokine gene expression by Epstein-Barr virus transformed human B cell lines. *Viral Immunol* **10(4)**:183-195
12. Gasmi, M., Glynn, J.M., Jin, M.J., Jolly, D.J., Yee, J.K. and Chen, S.T. 1999. Requirements for efficient production and transduction of human immunodeficiency virus type 1-based vectors. *J Virol* **73(3)**:1828-34

Patents

US20030161809A1: Compositions and methods for the transport of biologically active agents across cellular barriers; 2001-10-02